Darunavir

Brand Name: Prezista
Drug Class: Protease Inhibitors

Drug Description

Darunavir, also known as TMC114, is a nonpeptidic protease inhibitor (PI) containing 3(R),3a(S),6a(R)-bis-tetrahyrofuranyl urethane (bis-THF) and a sulfonamide isotere. [1]

HIV/AIDS-Related Uses

Darunavir was approved by the FDA on June 23, 2006, for use in combination with other antiretroviral agents for the treatment of HIV infection in adults.[2] It is indicated for the treatment of HIV infection in antiretroviral treatment-experienced adults, such as those infected with HIV-1 strains resistant to more than one PI.[3]

Darunavir is a second generation PI that is highly active in vitro against both wild-type and PI-resistant HIV. Darunavir is viewed as a potential substitute for PIs currently used in the treatment of HIV.[4]

Darunavir administered with a low-dose ritonavir booster (TMC114/r) is currently in Phase III clinical trials in both treatment-experienced and treatment-naive HIV-1 infected patients. In October 2005, Tibotec opened an expanded access program (EAP) for patients who have limited or no treatment options because of virologic failure or intolerance to multiple antiretroviral regimens.[5] [6] Additionally, a European EAP has begun following darunavir's approval by the FDA.[7]

Pharmacology

Darunavir is an inhibitor of the HIV-1 protease. It selectively inhibits the cleavage of HIV encoded Gag-Pol polyproteins in infected cells, thereby preventing the formation of mature virus particles.[8] The promising virologic profile of darunavir is the result of its unique chemical structure. The potency of darunavir against multidrug resistant viruses is believed to be due to a combination of its flexibility, extremely high affinity, and close fit within the substrate envelope.[9]

Evidence of efficacy of darunavir and ritonavir in antiretroviral treatment-experienced HIV infected adults is shown in analyses of interim 24-week data in two ongoing randomized, Phase IIb trials, TMC114-C213 and TMC114-C202. Both of these trials consisted of 2 parts: an initial partially-blinded, dose-finding part and a second long-term part in which all patients randomized to either darunavir and ritonavir or an investigator-selected antiretroviral regimen, then received the recommended dose of darunavir 600 mg and ritonavir 100 mg. Participants were required to have a baseline HIV RNA (viral load) of greater than 1000 copies/ml, had previous treatment with PIs, non-nucleoside reverse transcriptase inhibitors (NNRTIs), and nucleoside reverse transcriptase inhibitors (NRTIs), and have at least one primary PI mutation at screening, and to be currently taking a stable PI-containing regimen at screening for at least 8 weeks prior to study entry. Analyses included 318 patients in TMC114-C213 and 319 patients in TMC114-C202. At 24 weeks, the virologic response rate was evaluated in patients receiving darunavir and ritonavir plus an optimized background regimen (OBR) versus a control group receiving an investigator-selected PI-containing regimen plus an OBR.[10] Through 24 weeks of treatment, the proportion of patients whose HIV viral load was less than 400 copies/ml in the arm receiving darunavir and ritonavir compared to the comparator PI arm was 63% and 19%, respectively. In addition, the mean changes of plasma HIV viral load from baseline were -1.89 log10 copies/ml in the arm receiving darunavir and ritonavir and -0.48 log10 copies/ml for the comparator PI arm. The mean increase from baseline in CD4 cell counts was higher in the arm receiving darunavir and ritonavir (92 cells/mm3) than in the comparator PI arm (17 cells/mm3).[11]

The absolute oral bioavailability of a single 600 mg of darunavir alone and after coadministration with ritonavir 100 mg twice daily was 37% and 82%, respectively. Darunavir, coadministered with ritonavir 100 mg twice daily, was absorbed following oral administration with a time to peak plasma concentration (Tmax) of approximately 2.5 to 4 hours. When administered with food, the peak plasma concentration (Cmax) and area under the

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concentration-time curve (AUC) of darunavir, when coadministered with ritonavir, is approximately 30% higher relative to the fasting state. Therefore, darunavir coadministered with ritonavir should always be taken with food. Within the range of meals studied, darunavir exposure is similar.[12] In a study of 119 HIV infected patients, the mean 12-hour AUC was 61668 ng h/ml with darunavir 600 mg and ritonavir 100 mg twice-daily dosing. The median concentration at time of administration was 3539 ng/ml.[13]

The pharmacokinetics of darunavir have been studied in Phase II trials in healthy volunteers and in PI-experienced patients.[14] [15] In healthy volunteers, darunavir was rapidly absorbed; the time to maximum plasma concentration (Cmax) was 3 hours. Steady-state concentrations were reached within 3 days. Increasing doses of darunavir were administered alone or with ritonavir. Darunavir with ritonavir had a more favorable pharmacokinetic profile compared to darunavir alone. In the unboosted trial, the minimum plasma concentration (Cmin) at Day 14 ranged from 14 ng/ml to 142 ng/ml as the darunavir dose increased. Cmax ranged from 2,168 ng/ml to 8,040 ng/ml. In the ritonavir-boosted trial, Cmin at Day 14 ranged from 480 ng/ml to 1,486 ng/ml and Cmax ranged from 1,569 ng/ml to 5,453 ng/ml.[16]

Darunavir is in FDA Pregnancy Category B. There are no adequate and well-controlled studies conducted in pregnant women. Reproduction studies conducted with darunavir have shown no embryotoxicity or teratogenicity in mice, rats, and rabbits. Because of the limited bioavailability of darunavir in animals or dosing limitations, the AUCs were approximately 50% in mice and rats and 5% in rabbits of AUC in humans at the recommended clinical dose boosted with ritonavir.[17] In the rat pre-and postnatal development study, a reduction in pup body weight gain was observed with darunavir alone or in combination with ritonavir during lactation. This was due to exposure of the pups to drug substances via mother's milk. Sexual development, fertility, and mating performance of offspring were not affected by maternal treatment with darunavir alone or in combination with ritonavir. The maximal plasma exposures achieved in rats were approximately 50% of those obtained in humans at the recommended clinical dose boosted with ritonavir. To monitor maternal-fetal outcomes of pregnant women exposed to zidovudine (or other antiretrovirals), an Antiretroviral Pregnancy Registry has been established. Physicians may register patients online at http://www.APRegistry.com or by calling 1-800-258-4263. It is not known whether darunavir is excreted in human milk; it is excreted in the milk of lactating rats. Because of the potential for HIV transmission and for serious adverse effects from darunavir to the breastfed infant, women should be instructed not to breastfeed while taking darunavir.[18]

Darunavir binds primarily to plasma alpha 1-acid glycoprotein (AAG). Darunavir is approximately 95% bound to plasma proteins. In vitro experiments with human liver microsomes indicate that darunavir primarily undergoes oxidative metabolism. Darunavir is extensively metabolized by cytochrome P (CYP) enzymes, primarily by CYP3A. At least 3 oxidative metabolites of darunavir have been identified in humans; all showed activity that was at least 90% less than the activity of darunavir against wild-type HIV. A mass balance study in healthy volunteers showed that after single dose administration of 14-C-darunavir 400 mg coadministered with ritonavir 100 mg, the majority of the radioactivity in plasma was due to darunavir.[19] In the same mass balance study, approximately 79.5% and 13.9% of the administered dose of 14-C darunavir was recovered in the feces and urine, respectively. The terminal elimination half-life of darunavir was approximately 15 hours when darunavir was taken with ritonavir. After IV administration, the clearance of darunavir, administered alone and coadministered twice daily with ritonavir 100 mg, was 32.8 l/h and 5.9 l/h, respectively.[20] As darunavir and ritonavir are highly bound to plasma proteins, it is unlikely they will be significantly removed by hemodialysis or peritoneal dialysis.[21]

Darunavir exhibits activity against laboratory strains and clinical isolates of HIV-1 and laboratory strains of HIV-2 in acutely infected T cell lines, human peripheral blood mononuclear cells (PBMCs), and human monocytes/macrophages

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with median effective concentration (EC50) values ranging from 1.2 to 8.5 nM (0.7 to 5.0 ng/ml). Darunavir demonstrates antiviral activity in cell culture against a broad panel of HIV-1 groups M and O primary isolates with EC50 values ranging from less than 0.1 to 4.3 nM. The EC50 value of darunavir increases by a median factor of 5.4 in the presence of human serum.[22]

HIV-1 isolates with a decreased susceptibility to darunavir have been selected in cell culture and obtained from people treated with darunavir and ritonavir. Darunavir-resistant virus derived in cell culture from wild-type HIV had six- to 21-fold decreased susceptibility to darunavir and harbored 3 to 6 of these amino acid substitutions in protease: S37N/D, R41E/S/T, K55Q, K70E, A71T, T74S, V77I, I85V. Selection in cell culture mutations resulted in the overall emergence of 22 mutations in the protease gene. These darunavir-resistant viruses had at least 8 protease mutations at exhibited 50- to 641-fold decreases in darunavir susceptibility with final EC50 values ranging from 125 nM to 3461 nM.[23]

In analyses of 3 different Phase IIb studies using darunavir, multiple PI-resistant HIV-1 isolates were collected from highly treatment-experienced patients who received darunavir 600 mg and ritonavir 100 mg twice daily and experienced virologic failure either by rebound or by never being fully suppressed. These patients developed amino acid substitutions that were associated with decreased susceptibility to darunavir. The amino acid substitution V32I developed in greater than 20% of virologic failure isolates. Other substitutions that developed in 10% to 20% for darunavir and ritonavir virologic failure isolates occurred at amino acid positions I15, L33, I47, G73, and L89. The median darunavir phenotype (fold change from reference) of the virologic failure isolates was 21-fold at baseline and 94-fold at failure. Amino substitutions were also observed at the protease cleavage sites of some darunavir virologic failure isolates.[24]

Cross resistance to other PIs has been observed. Darunavir has a less than tenfold decreased susceptibility in cell culture against 90% of 3309 clinical isolates resistant to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, and/or tipranavir showing that viruses to these PIs remain susceptible to darunavir. Darunavir-resistant viruses were not susceptible to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, or saquinavir in cell culture. However, six of nine darunavir-resistant viruses selected in cell culture from PI-resistant viruses showed a fold change in EC50 values less than 3 for tipranavir, indicative of limited cross resistance between darunavir and tipranavir. Of the viruses isolated from patients experiencing virologic failure taking darunavir 600 mg and ritonavir 100 mg twice daily, greater than 50% were still susceptible to tipranavir, while less than 5% were susceptible to the other PIs.[25]

Cross resistance between darunavir and NNRTIs, NRTIs, and fusion inhibitors is unlikely because of the viral targets are different.[26]

Adverse Events/Toxicity

The most common treatment-emergent adverse events reported with the use of darunavir were diarrhea, nausea, headache, and nasopharyngitis.[27] (Because of the requirement for coadministration of ritonavir with darunavir, see the individual drug record for ritonavir for that drug's potential adverse effects for more information.) Abnormal liver and pancreatic function tests, abnormally high cholesterol and triglyceride levels, and decreases in white blood cell counts have also been reported.[28]

Darunavir administered with ritonavir should be used with caution with patients with hepatic impairment, as darunavir is primarily metabolized by the liver. There are no data regarding the use of darunavir and ritonavir when coadministered to patients with varying degrees of hepatic impairment; therefore, specific dosage recommendations cannot be made. Additionally, patients with pre-existing liver dysfunction, including chronic active hepatitis, can have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard of practice. If there is evidence of worsening of liver disease in such patients, interruption or

Adverse Events/Toxicity (cont.)

discontinuation of treatment must be considered.[29]

Redistribution of body fat, peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been observed in patients receiving antiretroviral therapy.[30]

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including darunavir. During the initial phase of combination antiretroviral treatment, a patient whose immune system improves may develop an inflammatory response to indolent or residual opportunistic infections, such as Mycobacterium avium infection, cytomegalovirus infections, Pneumocystis jirovecii pneumonia, or tuberculosis. Symptoms of immune reconstitution syndrome necessitate further evaluation and treatment.[31]

There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis in patients with hemophilia type A and B treated with PIs. In some additional factor VIII was given. In more than half of the reported cases, treatment with PIs was continued or reintroduced if treatment had been discontinued. A causal relationship between PI therapy and these episodes has not been established.[32]

The safety and tolerability of TMC114/r was evaluated in treatment-experienced patients taking doses of 400/100 mg once or twice daily, 800/100 mg once daily, or 600/100 mg twice daily. Most adverse events and laboratory abnormalities were mild to moderate and occurred with similar incidence across all groups, including a control PI group. The three most common adverse events in the 600/100 mg twice daily group were diarrhea, nausea, and headache; all three occurred with similar or less incidence than the control group. Overall, headache and diarrhea were the most common adverse reactions. Grade 3/4 reactions occurred in approximately 25% of each treatment and control group and included abnormal triglyceride, total cholesterol, and hepatic enzyme elevations. No differences were observed between treatment and control groups in overall adverse events, severe adverse events, or laboratory abnormalities.[33] [34]

Drug and Food Interactions

Darunavir must always be taken with ritonavir 100 mg in combination with other antiretroviral drugs.[35]

Coadministration of darunavir and ritonavir with efavirenz caused a decrease in darunavir AUC by 13% and minimum serum concentrations (Cmin) by 31%, while the AUC and Cmin of efavirenz increased by 21% and 17%, respectively. The clinical significance has not been established; however, this combination of drugs should be used with caution.[36]

Because didanosine must be administered on an empty stomach, didanosine should be administered one hour prior to or two hours after darunavir and ritonavir dosing with food.[37]

Coadminstration of darunavir and ritonavir with indinavir resulted in a serum concentration increase in both darunavir and indinavir. The appropriate dose of indinavir in combination with darunavir and ritonavir has not been established.[38]

Coadminstration of darunavir with lopinavir/ritonavir resulted in a 53% decrease in darunavir AUC. Coadminstration of darunavir and ritonavir with saquinavir resulted in a 26% decrease in darunavir AUC. Coadministration of these drugs with darunavir is not recommended.[39]

Both darunavir and ritonavir are both inhibitors of CYP3A. Coadministration of darunavir and ritonavir with drugs primarily metabolized by CYP3A may result in increased plasma concentrations of such drugs, which could increase or prolong their therapeutic effect and adverse effects.[40]

Carbamazepine, phenobarbital, phenytoin, and rifampin are inducers of CYP450 enzymes and should not be used in combination with darunavir and ritonavir. St. John's wort should also not be used concomitantly with darunavir and ritonavir. Coadministration of these drugs may cause significant decreases in darunavir plasma

Drug and Food Interactions (cont.)

concentrations and a loss of therapeutic effect to darunavir.[41]

Use of some HMG-CoA reductase inhibitors, including lovastatin and simvastatin, may require dose adjustment if taken concurrently with darunavir and ritonavir because of the potential of serious reactions such as myopathy, including rhabdomyolysis.[42] Coadminstration of darunavir and ritonavir with other HMG-CoA reductase inhibitors, such as atorvastatin and pravastatin, should be given at the lowest possible dose of the statin with careful patient monitoring.[43]

Caution must be used when antiarrhythmics, including bepridil, lidocaine, quinidine, and amiodarone, are used concurrently with darunavir and ritonavir. Concentrations of antiarrhythmic drugs may increase. Therapeutic concentration monitoring should be used, if available, to guide patient treatment.[44]

Concurrent use of darunavir and ritonavir with warfarin may decrease warfarin plasma concentrations, and patients should be monitored carefully if they are taking such a regimen.[45]

Concomitant use of trazodone and darunavir and ritonavir may increase plasma concentrations of trazodone, leading to nausea, dizziness, hypotension, and syncope. A lower dose of trazodone should be considered in patients who require this combination of drugs.[46]

Concurrent use of darunavir and ritonavir with clarithromycin may require dose adjustment of the clarithromycin dose in patients with impaired renal function.[47]

Ketoconazole and itraconazole are potent inhibitors as well as substrates of CYP3A. Plasma concentrations of these two drugs may increase in the presence of darunavir and ritonavir. When coadministation is required, the daily dose of azole should not exceed 200 mg.[48] Concurrent use of darunavir and ritonavir with voriconazole has not been studied. However, concomitant use of voriconazole and 100 mg ritonavir twice daily decreased voriconazole AUC by 39%. Therefore, patients receiving darunavir and ritonavir should not receive voriconazole unless the potential benefit outweighs the risk to the patient.[49]

Rifabutin is an inducer and substrate of CYP450 enzymes. Concomitant use of rifabutin with darunavir and ritonavir is expected to increase rifabutin plasma concentrations. It is recommended to administer rifabutin at a dosage of 150 mg rifabutin once every other day when coadministered with darunavir and ritonavir.[50]

Plasma concentrations of calcium channel blockers, including felodipine, nifedipine, and nicardipine, may increase when given concurrently with darunavir and ritonavir. Caution is warranted and clinical monitoring of patients is recommended.[51]

Plasma concentrations of immunosuppressants, including cyclosporine, tacrolimus, and sirolimus, may be increased when coadministered with darunavir and ritonavir. Therapeutic concentration monitoring for the immunosuppressive agent is recommended when these drugs are taken concurrently.[52]

When methadone is coadministered with darunavir and ritonavir, patients should be monitored for abstinence syndrome, as ritonavir is known to induce the metabolism of methadone, leading to a decrease in methadone's concentrations. An increase in methadone dosage may be considered based on the clinical response.[53]

Plasma concentrations of ethinyl estradiol may be decreased when it is used with darunavir and ritonavir due to the induction of its metabolism by ritonavir. Alternative or additional contraceptive measures should be used when estrogen-based contraceptives are coadministered with darunavir and ritonavir.[54]

Concomitant administration of darunavir and ritonavir with PDE-5 inhibitors, including sildenafil, vardenafil, and tadalafil, should be done with caution. PDE-5 inhibitor dosing should not exceed the doses as indicated by the manufacturer.[55]

Darunavir and ritonavir with selective serotonin reuptake inhibitors (SSRIs) sertraline and paroxetine should be taken concomitantly with caution. The recommended approach is a careful

Drug and Food Interactions (cont.)

dose titration of the SSRI based on a clinical assessment of antidepressant response. In addition, patients on a stable dose of sertraline and paroxetine who start treatment with darunavir and ritonavir should be monitored for antidepressant response.[56]

Contraindications

Darunavir must always be taken with ritonavir 100 mg in combination with other antiretroviral drugs.[57]

Both darunavir and ritonavir are both inhibitors of CYP3A. Coadministration of darunavir and ritonavir with drugs primarily metabolized by CYP3A may result in increased plasma concentrations of such drugs, which could increase or prolong their therapeutic effect and adverse effects.[58]

Clinical Trials

For information on clinical trials that involve Darunavir, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: Darunavir AND HIV Infections.

Dosing Information

Mode of Delivery: Oral.[59]

Dosage Form: Tablets containing 300 mg darunavir.[60]

The recommended daily dose of darunavir is 600 mg (two 300 mg tablets) taken with ritonavir 100 mg twice daily with food.[61]

If a patient misses a dose of darunavir and ritonavir by more than 6 hours, the patient should be told to wait and then take the next dose of darunavir and ritonavir at the regularly scheduled time. If the patient misses a dose by less than 6 hours, the patient should be told to take darunavir and ritonavir immediately, then take the next dose at the regularly scheduled time. If a dose of darunavir and ritonavir is skipped, the patient should not double the next dose. Patients should not take more or less than the prescribed dose of darunavir or ritonavir at any one time.[62]

Darunavir and ritonavir doses of 400/100 mg to 800/100 mg have been studied in clinical trials. A darunavir and ritonavir dosage of 600/100 mg twice daily is the dose that has been chosen for continued study. 200, 300, and 400 mg tablets of darunavir have been or are currently being used in clinical studies but are not expected to be available to the general public.[63] [64] [65]

Storage: Store tablets at 25 C (77 F); excursions permitted at 15 C to 30 C (59 F to 86 F).[66]

Chemistry

CAS Name: (3R,3aS,6aR)-Hexahydrofuro(2,3-b)furan-3-yl N-((1S,2R)-1-benzyl-2-hydroxy-3-(N1-isobutylsulfanilamido)propyl)carbamate[67]

CAS Number: 618109-00-5[68]

206361-99-1[69]

Molecular formula: C27-H37-N3-O7-S[70]

C59.2%,H6.8%,N7.7%,O20.5%,S5.8%[71]

Molecular weight: 593.73[72]

Physical Description: White to off-white powder.[73]

Solubility: Approximately 0.15 mg/ml in water at 20 C.[74]

Other Names

TMC 114[75]

TMC114[76]

Further Reading

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Manufacturer Information

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For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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